

## II

# EXPERIMENTAL CONTRIBUTION TO THE STUDY OF ANTISYPHILITIC HYPERTHERMY PRODUCED BY PHYSICAL AGENTS

### DISCUSSION

DR. BECK, who has been doing experimental work at the Dreadnought Hospital, Greenwich, was invited to open the discussion. He said that from the mass of evidence which Professor Bessemans had brought together it was clear that the heat factor was of paramount importance in the cure of syphilis. He had also made clear the limitations of this method by saying that spirochætes in some parts of the body might acquire some high degree of thermo-resistance, possibly a degree which could not be reached in the human tissue without danger. Recently the speaker had had occasion to carry out experiments on syphilitic mice, and during those experiments he obtained data which seemed to point to the fact that it was possible to get fairly regular sterilisation of the lymph glands of the mice if sufficient amounts of heat were given.

He wished in the first place to explain why he chose mice for the experiment. The syphilitic infection in mice was of the latent type. Infection with virulent syphilitic material did not produce any manifest lesions. The spirochætes spread over the whole body ; they might be found by histological methods in nearly all the tissues, and Professor Bessemans had shown that they could be detected by darkground methods in the brain. He chose the mouse because he thought it would be interesting to study the influence of heat on this type of latent infection where no great tissue response took place against the infecting spirochætes. A second reason was that the mouse seemed to be a useful animal for comparing the resistance of spirochætes in the brain and in lymphatic glands. He had to admit that there was a great difference between spirochætes in the brain of a mouse and in the

brain of a general paralytic. The spirochætes in the latter produced lesions, but in the mouse brain no lesions were to be found. He thought that the question of the existence of a special brain-adapted spirochæte might be usefully solved by examining the mouse.

He first tried to get as high a fever peak as possible. For producing fever he kept the mice in a kind of heat box. The heat was produced by a carbon filament lamp. The mice were kept in small compartments closed by shutters. With this method it was possible to produce rather sudden rises of temperature in the mouse if the outer temperature was a high one. He had been able to reach in from five to eight minutes rectal temperatures in mice up to 106 and 108° F., sometimes even more. With these applications of high heat, he could not extend the duration of the sittings for a very long time. He gave at first only a quarter of an hour, and repeated this either on consecutive days or every other day for five to twenty-five days. The result of these short sittings was shown on a table. After the treatment was ended the mice were killed and their lymph-glands and brain transferred into the testes of fresh rabbits for the control of spirochætes. At the same time mice infected, but untreated, were also killed and their lymph glands and brain transferred to normal rabbits. He varied the number of heatings with intention, in order to bring out any possible difference in heat resistance of brain and lymph spirochætes. Taking a group of five mice which have all had a great number (fourteen to twenty-five) of heatings, there were two which had been sterilised in lymph glands and in brain, one in which the brain only had been sterilised, and the other two remained positive. Mice apparently having the same amount of treatment became positive in one case and negative in another. He thought the difference might be due to the fact that the amount of heat given was not much above the minimal dose, and these inconsistencies might be only an expression of the normal biological variability.

He undertook a second series of experiments in which he wanted to go well above the necessary amount of heat. In these mice the duration of the sitting was changed to one of four hours' duration, and the number of sittings varied between thirteen and fifteen heatings. He thought this type of heat might be more comparable to the type

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of the malaria fever than that obtained with the very short sittings. The temperature was controlled (by rectum) every half hour. He tried also to make exact measurements of the brain temperature by placing a pair of thermo-couples into the brain, but this proved to be impracticable because the introduction of the thermo-couple was followed by a sudden drop of temperature due to the shock produced. In this group of animals better results were forthcoming. The controls became positive, their lymph glands being always positive, the brain in some cases remaining negative. Of five mice treated with such prolonged heatings four were sterilised in the lymph glands and brain, but one mouse which had quite a long treatment, the total duration of fever being fifty-six hours, still proved to be positive.

There was no doubt that the heat was the main factor, but there must be something in the host itself which might in certain circumstances modify the effect of heat. Not much was known about tissue immunity in syphilis. But it was possible that tissue processes influenced the result of heating. From the researches of an Italian worker (Benvenuti) there seemed to be some evidence of an increased inflammatory reaction in the brain of general paralytics during malarial fever and the interference of such a local (tissue-) factor may be responsible for the difference in the results obtained by treatment with artificial fever.

DR. W. D. NICOL, after thanking Professor Bessemans for his lucid exposition, said that he doubted whether he should be speaking at all because he was a protagonist of malarial therapy against electro-pyrexia. But he could only speak as a clinician. In assessing clinical results the condition of the patient, the time that had elapsed between the onset of symptoms and the therapeutic administration had all to be taken into account. If one could get statistics from general hospitals, where cases were treated much earlier than in mental hospitals, he did not think the results would be comparable at all. Therefore one wondered whether there was a better method of trying to assess the value of any particular procedure. At Horton they had been examining the serological results after treatment, and there was no doubt that in from 80 to 85 per cent. the cerebrospinal fluid became negative. At Horton, save for two years,

the treatment, which must cover now a thousand cases or more, had been entirely confined to malaria, and no after-treatment was given in the way of arsenicals or tryparsamide. In reading the literature with regard to electro-pyrexia, it was very difficult to find records of cases treated by that method *per se*. In nearly all cases reported supplementary courses of tryparsamide or heavy metal therapy were recommended: was this really necessary?

Then came the question of the length of treatment. Ten sessions of five hours each were recommended at intervals of four to seven days. In some of the Horton cases it should be possible to produce evidence of some in which not more than eight peaks of fever had been given, and by the employment of certain species of malaria, the temperature was not raised above 104° F. and in these cases it was hoped to show that the Wassermann of the cerebrospinal fluid had been either reduced or rendered negative. What one advocated from the point of view of the clinician was that the workers, both with malaria and with electro-pyrexia, should try the efficacy of a certain treatment *per se* and not supplement it with tryparsamide or other heavy metal therapy. They should find out in that way the minimum amount of treatment that was necessary. The present habit of over-treating cases with consequent waste of time and money was to be deprecated.

MR. AMBROSE KING said it was clear that the important experimental work on the effect of heat on *Treponema pallidum* and on the lesions of animal and human syphilis, to which Dr. Bessemans and his associates had contributed so much, indicated the probability of a notable advance in methods of treating the disease. These experiments had formed the starting-point of a number of clinical investigations as to the value of artificially induced pyrexia as an additional method of treating human syphilis in all its stages. The application of this method had extended from the limited field of general paralysis to other types of neurosyphilis, to some resistant forms of late tertiary syphilis in which chemotherapy had proved ineffective, and to the earlier manifestations of the disease when the ordinary chemical remedies were not tolerated. In a recent visit to the Kettering Institute he was impressed with the effects of combined chemical therapy

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and artificial fever, not only in producing rapid healing of external syphilitic lesions but in reversing positive serological reactions which had proved irreversible by chemotherapy alone. In view of the work of Simpson and of Neymann, consideration must be given to the possibility that the combination of hyperthermia with chemotherapy would in time prove to be effective in shortening the necessary period of treatment of early syphilis. Of course a number of years must pass before it could be known whether these hopes were to be realised and all premature claims should be rejected. Meanwhile it was surely time that, in this country, some belated effort were made to contribute a share to this investigation.

Dr. Bessemans was also to be congratulated on his efforts to bring order to the confused terminology which had attached itself to this subject. It was anticipated that his remarks as to his experiences with various types of thermometers would be of great value to those who favoured inductothermy or radiothermy as methods of inducing fever.

COLONEL E. T. BURKE recalled a poem of his schooldays which began : " I sprang to the stirrup and Joris and he," which told how proudly they brought the good news from Ghent. Nobody seemed to know what that particular good news was, why it was being exported, or the identity of the mysterious triumvirate. It appeared to be much ado about nothing. But the " good news from Ghent " which they had had that evening was quite a different proposition. They knew the messenger and were familiar with his work, and there was nothing obscure in the paper he had read. He did not think there could be any doubt that thermogenic procedures were destined to play an ever-increasing *rôle* in the field of venereology. That *rôle* was bound to be a dual one, prophylactic on the one hand and curative on the other. On the curative side it was likely to be most effective, first in neuro-syphilis, and secondly in dealing with the complications of gonorrhœa. From the purely prophylactic point of view he considered it to be a powerful instrument in preventing a person suffering from early syphilis from developing syphilis of the central nervous system. In the male sex in the vast majority of cases of acute or early syphilis there was some degree of involvement of the central nervous system or its supporting structures. It was

certainly prudent to assume that in all cases of acute syphilis, even in the presence of an apparently negative cerebrospinal fluid, the central nervous system was involved to some extent. It was necessary to keep every possible means of chemotherapy and other measures available, including the various thermogenic procedures, which had a proved value so far as prevention was concerned. Malaria seemed quite unsuitable for protecting the central nervous system in persons suffering from acute syphilis. The majority of such persons were young and in active employment. Malaria therapy meant their hospitalisation for several weeks and a prolonged period of convalescence. It would be difficult, because of these disadvantages, to persuade the average clinic adult patient to undergo malarial treatment; on the other hand, in the case of thermogenic treatment none of these drawbacks applied. It would be much easier to get a patient to enter the "hot box" than to go into a mental hospital, which did have a certain stigma attached to it.

He desired to put forward the proposition that the effect of heat was to create some change in the deep tissue metabolism of the patient resulting in the production of something which was lethal to the organism. The results of heat applied locally to the chancre seemed to bear that out. The fever in malaria therapy was after all to a great extent only accidental and incidental; it was merely an indication that the metabolic change had been brought about. That change could, and often did, occur without any fever at all. Most of them could call to mind cases in which, after inoculation with malaria, there was no rigor and yet the clinical and serological results were as good as, or better than in the patients who had had actual malarial attacks. He suggested that heat applied to the tissues either locally or generally, caused dead lipo-protein material to be thrown into the circulation, and this stimulated local and generally antibody ferment production—a lipo-proteolytic ferment. In malaria there was, first of all, the destruction of erythrocytes by the malarial parasite and, secondly, after the administration of quinine the destruction of the malarial parasites themselves. Both these things caused dead lipo-protein material to appear in the circulation, and this acted as an antigen for the production of an antibody or amboceptor towards lipoid-rich cells or

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parasites such as the *Treponema pallidum*. Whatever the reason there was no doubt that heat was a valuable adjunct to chemotherapy, but there was something much more important than a heat element involved.

DR. E. L. HUTTON said that in view of the detailed experiments Professor Bessemans had produced, it was perhaps a little rash of her to query his statement that it was probably the fever *per se* which was responsible for the destruction of the infective organism. At the same time, she felt that the question was still open to doubt. It was not without significance that one of the most effective methods for treating neuro-syphilis was by means of a disease which in itself had a very high immunity-producing factor, and although she was fully aware that it had never been proved that there was any immunity produced by the spirochæte, and also that the Wassermann reaction and other allied tests were not true immunity reactions owing to the fact that the antibody which could be used was entirely non-specific, yet she thought it could not be denied that the Wassermann and other phenomena were closely allied to immunity response. This led one to the question as to the part played by fever in infectious diseases. Was fever merely a side effect or was it part of the body's defence mechanism against pathogenic organisms? If the fever itself was capable of killing off noxious organisms, then it did seem regrettable that in a disease with a highly heat-susceptible organism like the spirochæte, the body did not respond to the infection by running a high temperature. In pneumonia on the other hand, the pneumococcus was not very heat-susceptible, but the patient often ran a high temperature over a relatively long period, at the end of which time the fever subsided suddenly, coinciding with the crisis. It was known that at the crisis there was a sudden increase in the amount of antibodies present in the serum. Was it not possible therefore that the fever in these diseases was a mechanism promoting the production of antibodies, possibly by means of the increased metabolism which accompanies high temperature? H. G. Wells\* in his book on immunity, stated, "It is highly possible that many therapeutic agents may act by stimulating the tissues to increased formation of specific antibodies, *e.g.* arsenic, mercury and other metals, heliotherapy, hæmor-

\* H. Gideon Wells. "The Chemical Aspects of Immunity," 1929, p. 106.

rhage or phlebotomy, hot baths." Neymann\* in his description of 7 cases of primary syphilis who were treated by diathermy, stated that in those cases with a negative or only weakly positive Wassermann reaction the effect of the fever was to make the test strongly positive, which he himself thought might be due to massive destruction of the treponema and release of their endotoxins, *so producing an immediate increase in syphilitic amboceptor formation*. Might it not be that here and in the experiments to-night described by Professor Bessemans, where the organism had already been in the tissues for several days before the heat was applied, immunity responses in the host had been evoked and the heat acted by giving a certain impetus to the defensive mechanism of the tissues?

DR. W. KERR RUSSELL said that physically produced artificial fever was started at the National Temperance Hospital in May, 1935, and 87 cases had been treated and had received 734 treatments. He had installed and in turn discarded certain apparatus. He used firstly the pyrotherm with a condenser field, which was unsatisfactory. Next he tried inductothermy with an insulated treatment bag, but this was rather uncomfortable for the patient. More recently he had tried inductothermy with the special cabinet made by the Victor X-ray Co., which had the induced electro-magnetic field plus infra-red rays. Other devices had also been tried. Most of the cases treated had been those of disseminated sclerosis. Another group was early rheumatoid arthritis, but perhaps the only group of any interest from the point of view of the present discussion was the gonococcal group, of which there had been only 10 cases. In one case of arthritis the primary infection had occurred twenty-four years previously. Local ultra short-wave treatment was tried for a considerable periods without benefit. Then four electro-pyrexia treatments were given using temperatures of 106.5° F. ; maintaining them for six hours. After the treatment the swelling of all the joints had subsided and there was an excellent ultimate result. Another patient with arthritis had previously received seven T.A.B. injections, and there was some improvement, but after a further three injections no further improvement. That patient made an

\* C. S. Neymann. *Am. J. Psych.*, Nov. 1936. Vol. 93.



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excellent recovery with four electro-pyrexia treatments. There were two cases of prostatitis, two of cystitis, one of urethritis, and one salpingitis case. The latter was interesting because the temperature became normal and the abdominal tenderness disappeared, but the treatment was not a success because the patient only had eighteen hours of hyperpyrexia whereas it has been found that the thermal death time for the gonococcus at a temperature of  $106.7^{\circ}$  F. varies from six to thirty-four hours.

DR. MARY LISTON, said, I have listened to this address with great interest, but there is one question I would like to ask because I think the answer would help us to select the best therapeutic agents. The question is, How do spirochætes act on the host, is there unquestionable scientific evidence that they can produce toxins?

"The syphilitic virus" is a term we hear often spoken about. What is it?

I tried to find this out, and in one book of authority, (*M.R.C.*, 8), I read: "The actual virus" was found to be "a spiral organism of characteristic appearance." But previous to this statement it was stated: "How the pathogenic spirochætes act is very difficult to explain for hitherto there is no satisfactory evidence that their action is due to toxins." In another bacteriological book (Muir and Ritchie), I found that "fluid containing the virus" lost its infectivity when passed through a filter, and it further stated, therefore the virus does not belong to the ultra-microscopic group of organisms. Is there any need to say that if *S. pallida* is the virus?

If such words are used clinicians are apt to think that a poisonous substance has been found and cease to take any further interest as to what causes the inflammatory reaction such as a gumma.

We do know that bacterial proteins alone without living organisms can produce a tubercle. How is it that nothing further has been found regarding the spirochæte? Besides finding spirochætes in a syphilitic lesion we do find bacteria also. We know that spirochætes are altered in some way when they are acted upon by antibody in the blood serum or tissues so that bacteria or other particular material adhere to them. We express *S. pallida* from the tissues, whereas many other spirochætes are simply on the surface of the body. Can this adhesion phenomenon not account for the apparent toxicity of some spirochætes?

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Bacterial toxins also have selective affinity for certain tissues. Unless we find the true cause therapy will fail.

DR. ERNEST MAYER-NEVILLE said: In all microbic infections we must not forget the possibility that what we usually hold to be the only and exclusive causative agent may only represent a phase in a chain of possible events and conditions, and that it would be well to remember the work of Dr. Antoine Béchamp in this respect who had pointed out far-reaching observations and facts long before Pasteur (who first contradicted him and then plagiarised him) had popularised (though on less cogent grounds) the microbic nature of infection.

I do not mean that syphilis is not due to *Spirochaeta pall.*, but that I suspect the organism to have various forms, possibly as a result of various life-cycles. I was myself a student at Berlin University when *Spirochaeta pall.* was first demonstrated there, and have heard many arguments about it. I also advocated the idea of treating syphilis by means of artificially produced heat plus medical treatment as far back as 1922 (I make no claim of priority).

DR. H. C. G. SEMON asked whether the last speaker had taken the temperature of the subjects who were exposed to the sun in those climates, and whether he suggested that the temperatures were anything like 120° F.

DR. MAYER-NEVILLE said that the temperature reached that height on occasion.

DR. BESSEMANS, in reply, said that he had been particularly interested in the experiments of Dr. Beck and congratulated him on his work. Mice were animals which did not support general heating very easily. Dr. Beck had said that syphilitic infection of the mouse was always non-apparent. In one case in his own laboratory, however, a chancre had been obtained in a mouse. He believed there were only two cases of this kind recorded in the literature, his own and one reported by Kolmer and Kast. In his case it was possible to transfer the chancre to a second mouse. He agreed with the clinicians that with heat there was always a double action. It acted directly on the organism and also on the host, and all the defensive reactions of the host were stimulated. He closed by thanking all who had taken part in the discussion for the interest they had shown in his paper, and he hoped clinicians and laboratory workers would continue working on the problem.